Project title: **"Engineering and Targeting Recurrent Aneuploidy in Cancer using a novel method"**

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Research Group: **Cancer Dynamics**

Our lab programme spans basic, translational and clinical science and we study both tumour initiation and progression in the context of renal cell cancer and melanoma. We combine deep phenotyping of patient samples, mathematical simulations, per-clinical modelling (including IPSC, organoids and genome engineering, as well as patient-derived tissue fragments). We will fit the exact project to best suit the candidate and their interest and aptitude and both wet lab and dry lab projects are feasible. An example project focuses on Aneuploidy, imbalanced chromosome copy number, is a hallmark of cancer. Different cancer types present distinct recurrent patterns of aneuploidies, highlighting their context-dependent selection and functional significance[1]. However, it has been challenging to efficiently and precisely engineer targeted aneuploidy in relevant preclinical models[2], impeding their functional interrogation. In the Turajlic Lab, we have developed CRISPR-Taiji (CRISPRt), a novel chromosome-specific aneuploidy engineering tool that disrupts mitotic chromosome segregation using catalytically dead Cas9 in a chromosome-specific manner. This allows us to engineer specific recurrent aneuploidy events in preclinical models, enabling molecular and functional interrogation of their role in cancer.
Clear cell renal cell carcinoma (ccRCC) is the most common kidney cancer, with rising incidence and about 150,000 global deaths annually. Its initiation is almost universally driven by chromosome 3(p) loss[3], while metastases are strongly associated with the loss of chromosome 9(p) and chromosome 14(q)[4]. Our recent RNA-seq analyses of ccRCC tumour regions with these aneuploidies revealed significant pro-tumour transcriptomic changes, reinforcing their functional relevance in disease progression[5].
This project will combine our unique clinical resources from the TRACERx Renal study (http://tracerx.co.uk/studies/renal/) with our advancements in aneuploidy engineering to systematically characterize these events and identify therapeutic vulnerabilities.

Key Objectives

- Model Establishment – Establish normal kidney and ccRCC organoids from fresh surgical specimens.
- Genetic Engineering – Generate isogenic aneuploidy organoid models using CRISPRt and other genetic engineering techniques.
- Characterisation – Apply multiomics profiling and functional assays to characterize the pro-tumour roles of chromosome 3(p), 9(p) and 14(q) loss.
- Co-culture establishment with immune cells to investigate the role of cGAS/STING signalling and immunosuppression in metastases
- Therapeutic Development – Rational design and validate novel therapeutic based on the characterisation data and perform CRISPR or drug screens to identify additional therapeutic vulnerabilities and synthetic lethal interactions.

References

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3 Mitchell, T. J. *et al.* Timing the Landmark Events in the Evolution of Clear Cell Renal Cell Cancer: TRACERx Renal. *Cell* **173**, 611-623.e617 (2018). https://doi.org:10.1016/j.cell.2018.02.020

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